

Figure 1

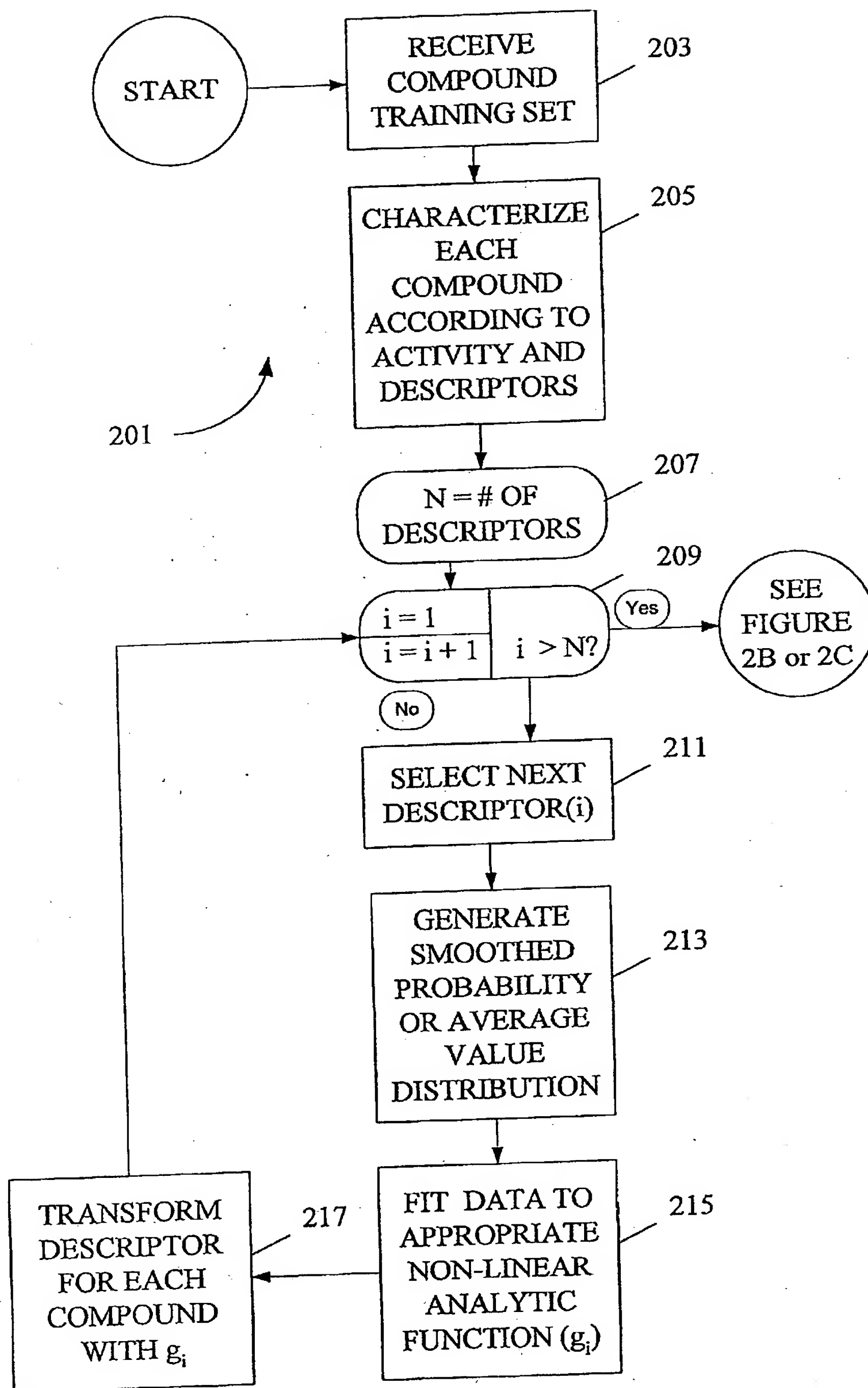


FIGURE 2A

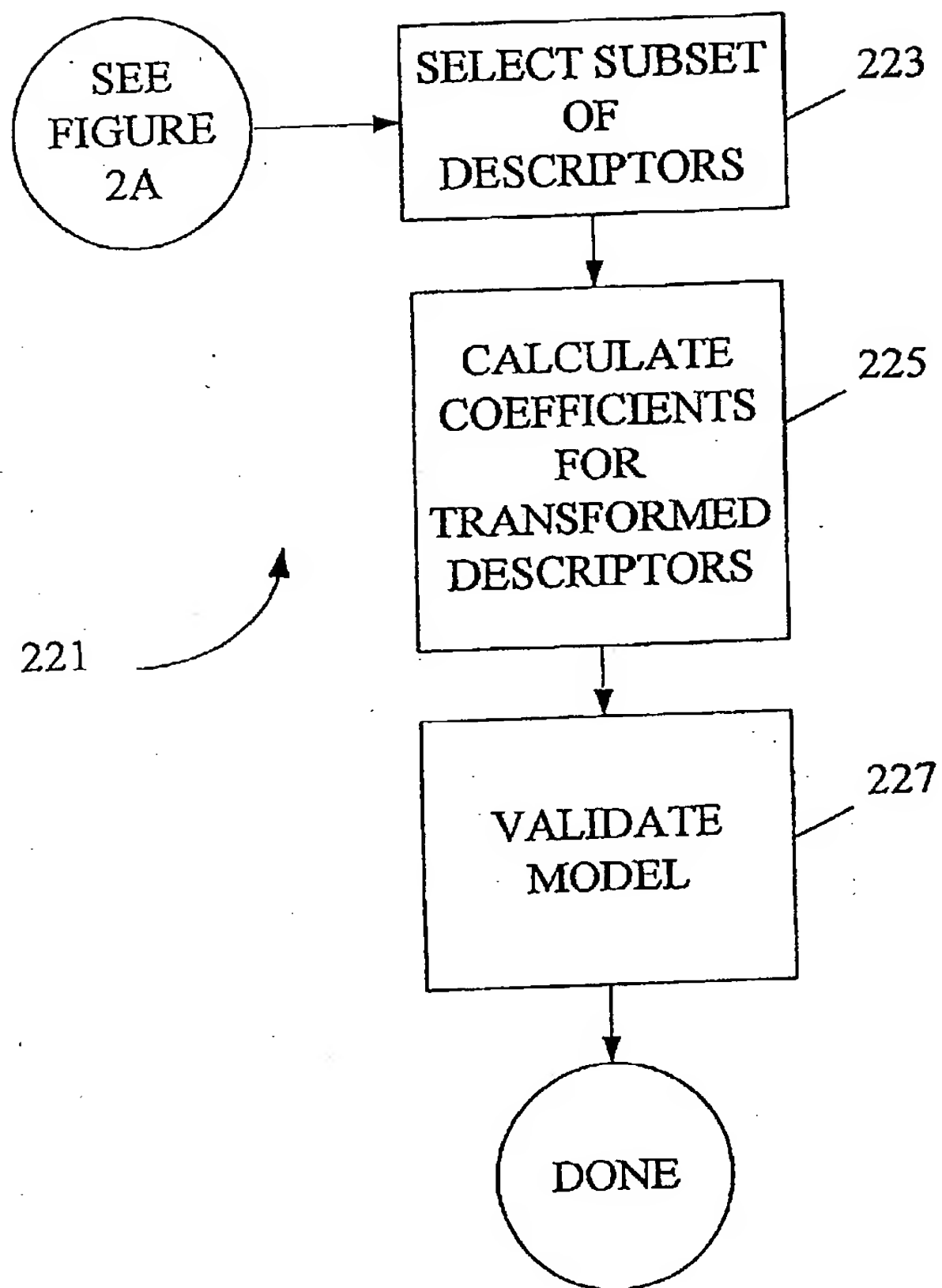


FIGURE 2B

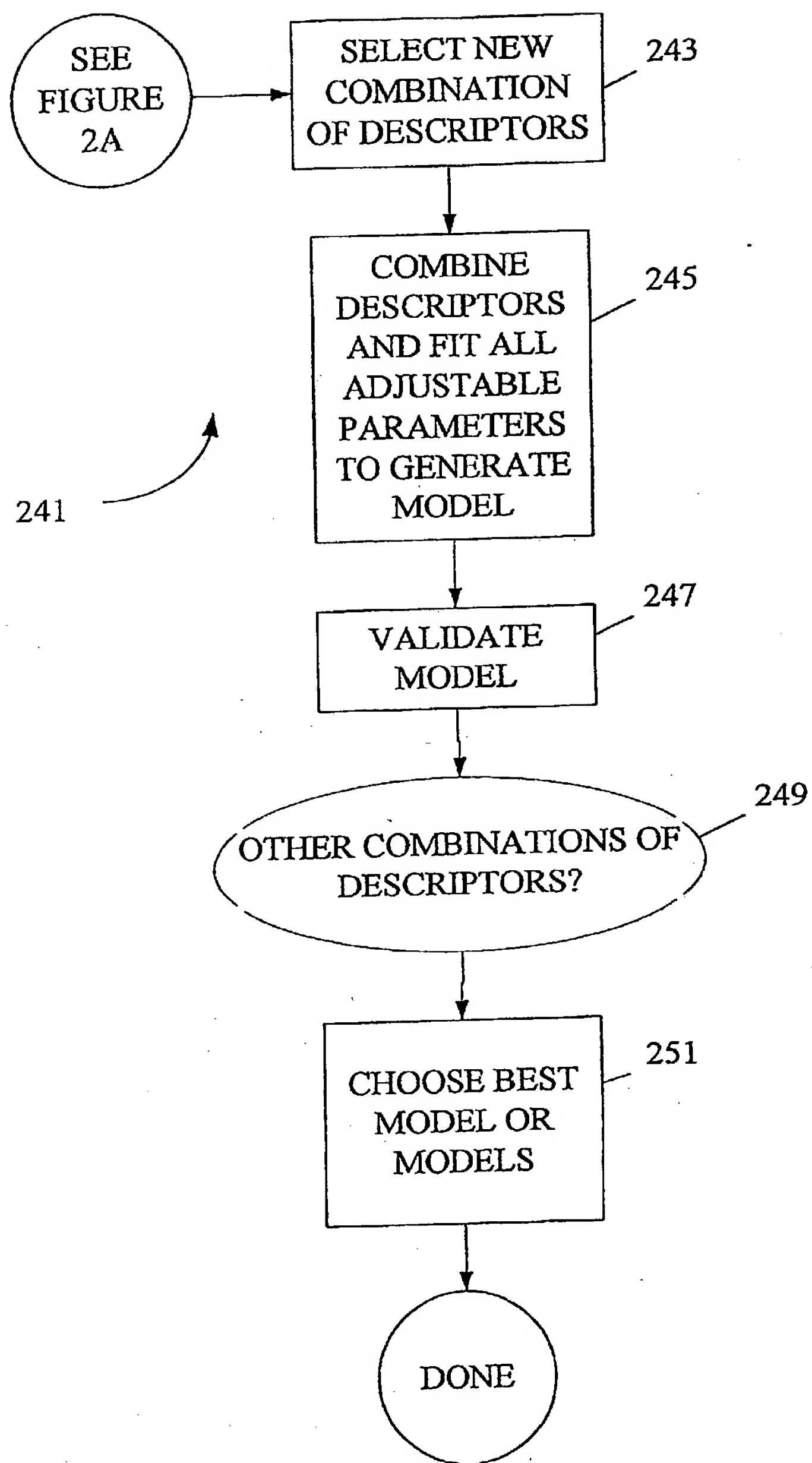
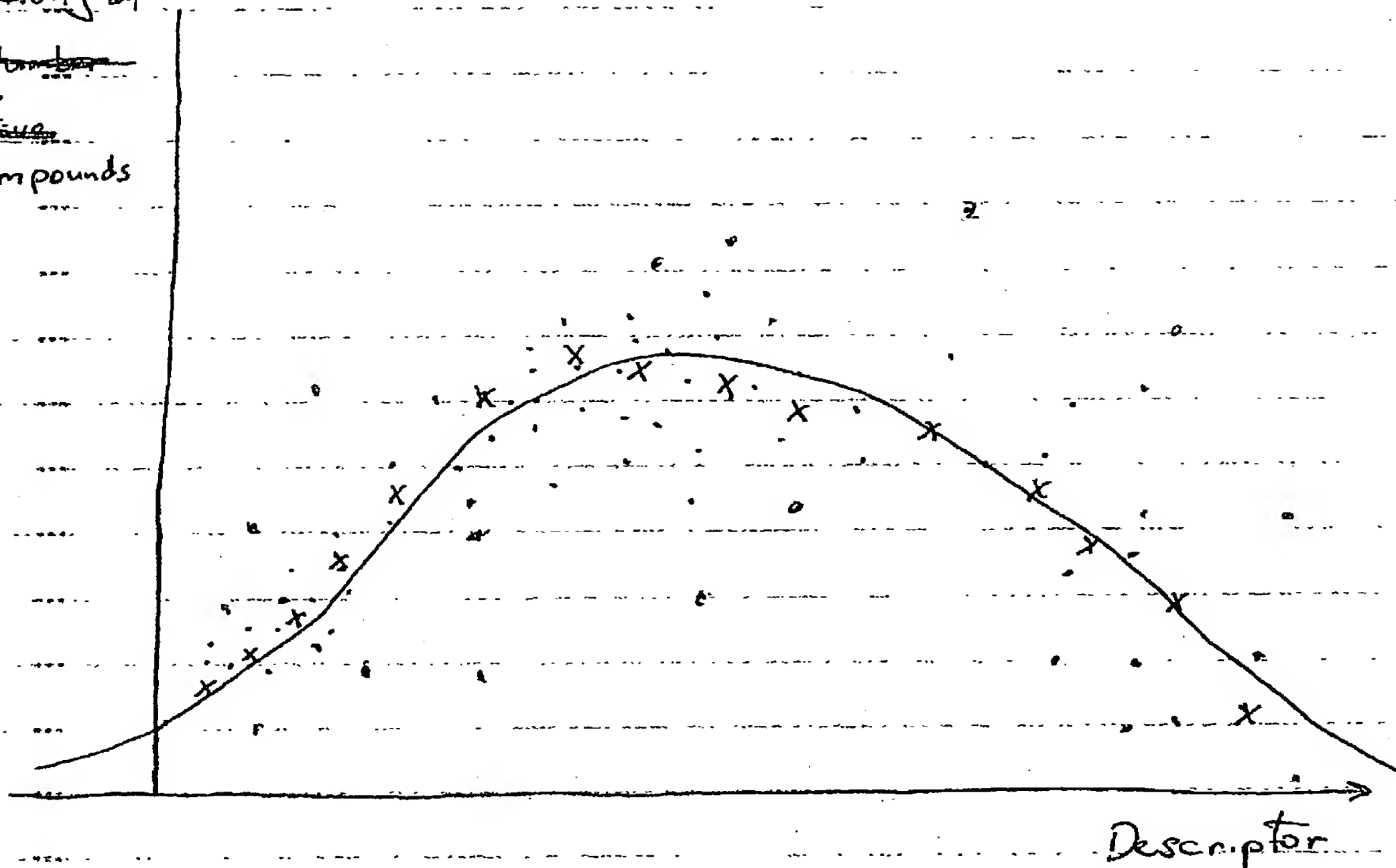


FIGURE 2C

Activity of
~~Number~~
~~of~~
~~Active~~
 Compounds

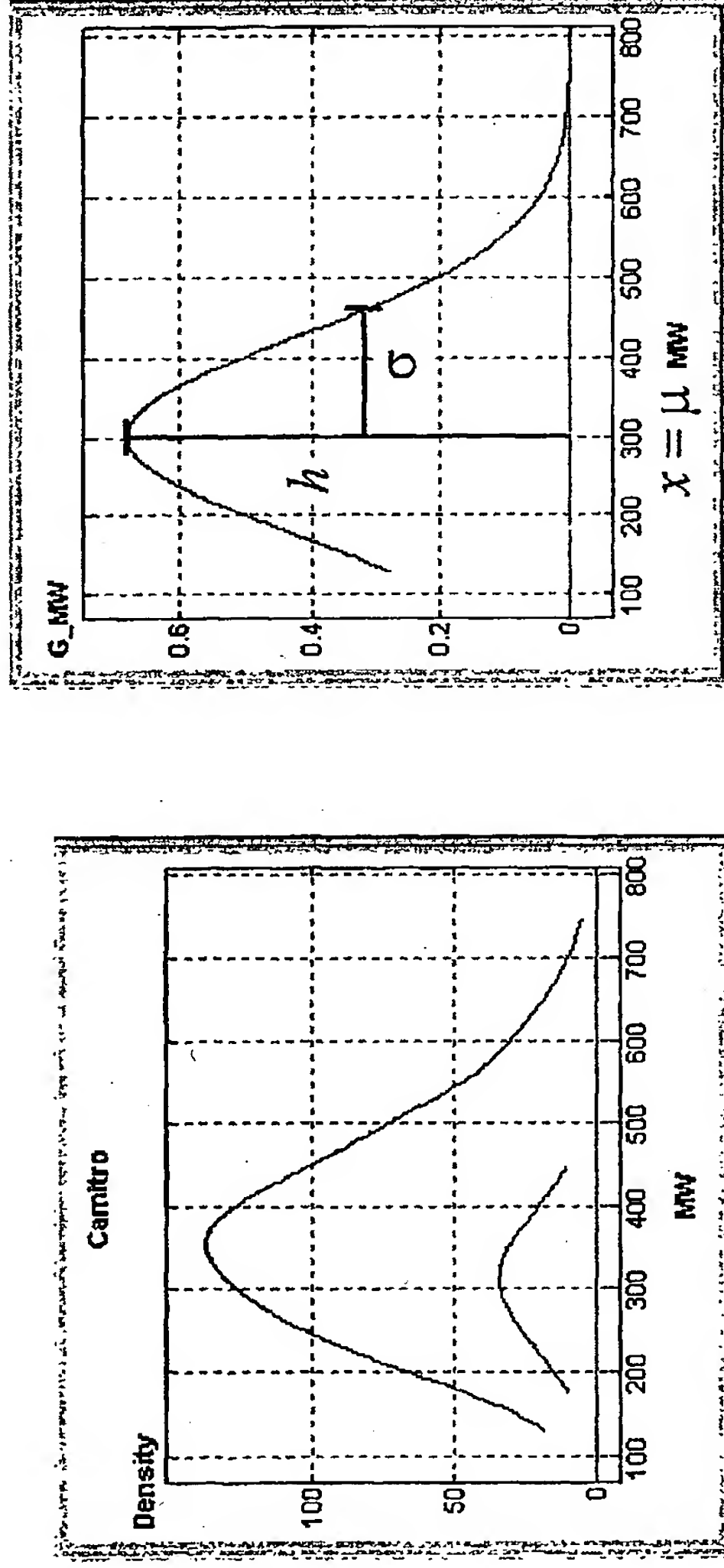
10034653-121504



• = data point
 x - smoothed point
 — - Smoothed data
 fit to a
 transformation
 function
 Legend

Figure 3

Optimum Molecular Weight



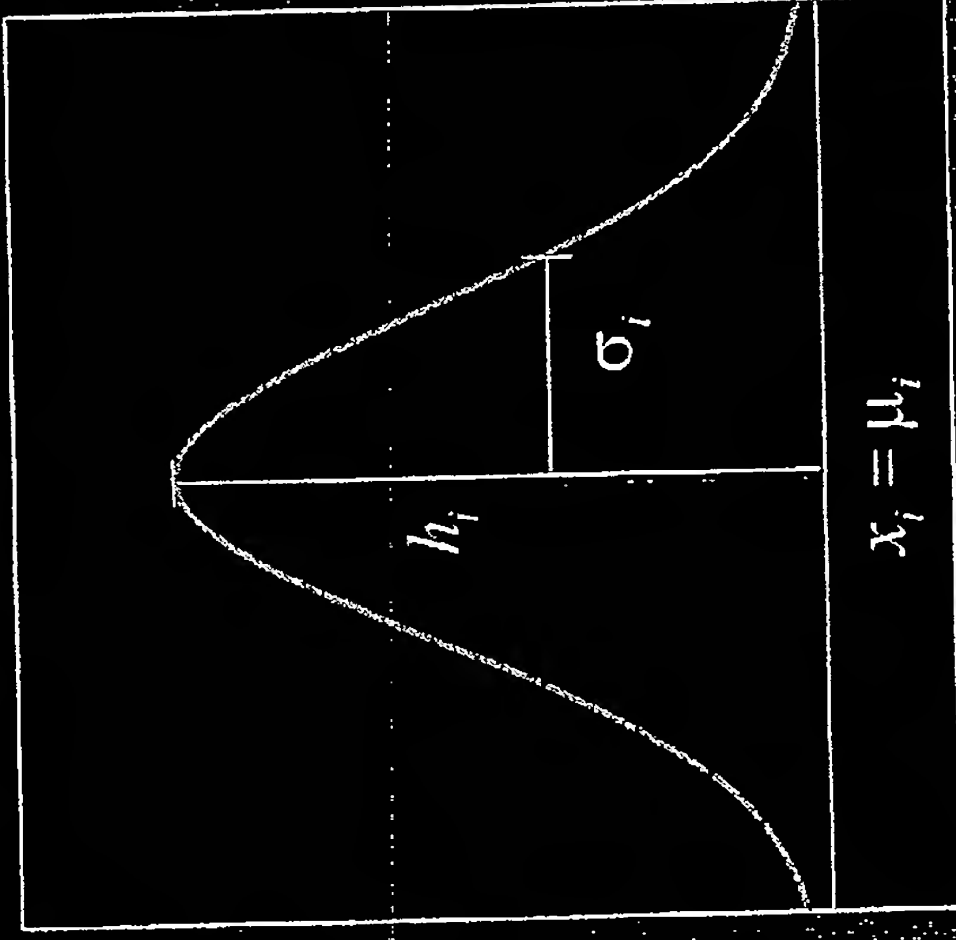
$$g(x) = h e^{-\frac{(x-\mu)^2}{4\sigma^2}}$$

Figure 4A
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N-Dimensional Gaussian Modeling

Additive

$$g(x_{i..N}) = \frac{1}{N} \sum_{i=1}^N h_i e^{-\frac{(x_i - \mu_i)^2}{4\sigma_i^2}}$$



Multiplicative

$$g(x_{i..N}) = h e^{-\frac{1}{N} \sum_{i=1}^N (x_i - \mu_i)^2 / 4\sigma_i^2}$$

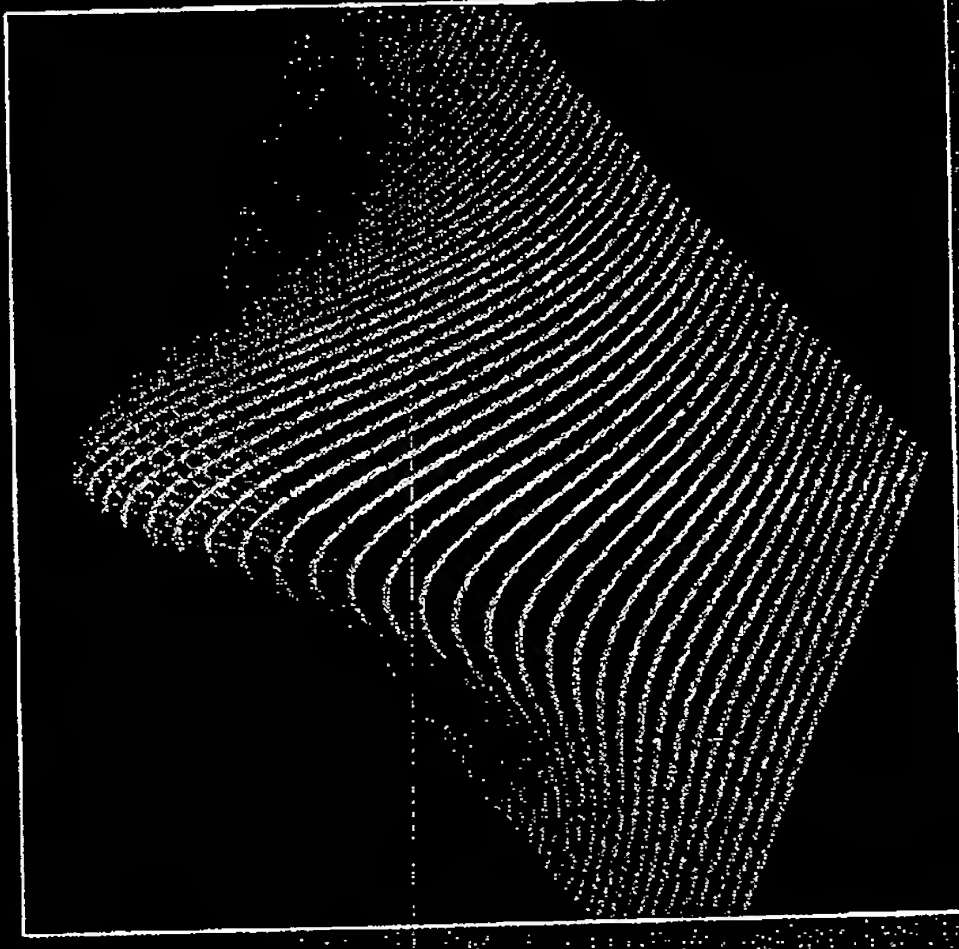


Figure 4 B

Cambridge

Optimization Function

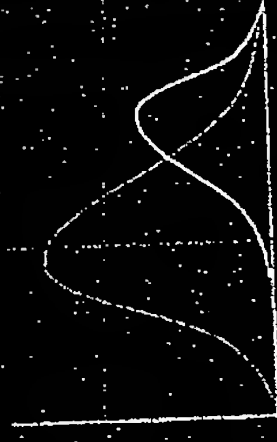
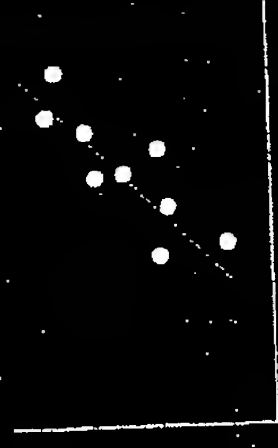
$$g(x, \mu, \sigma, h, t) = t + he^{-\sum_{k=1}^{N_x} (x_k - \mu_k)^2 / 4\sigma_k^2}$$

$$f = S_{inh} \left[\frac{1}{N_{inh}} \sum_{i=1}^{N_{inh}} (g(X_i, \mu, \sigma, h, t) - y_i)^2 \right] + S_{drug} \left[\frac{1}{N_{drug}} \sum_{j=1}^{N_{drug}} g(X_j, \mu, \sigma, h, t) - \bar{y}_{drug} \right]^2 + S_{fit} \left[\sigma_y^2 \sum_{k=1}^{N_x} \left(\frac{\mu_k - \mu_{0,k}}{range(X_k^T)} \right)^2 + (t - t_0)^2 \right]$$

Mean of the Squared Errors
of Inhibitor Affinity

Squared Error of the Means
of Drug Affinity

Constraints to prevent
Overfitting



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Figure 4C

Initial Values for Optimization

$$t_0 = \min(y)$$

$$h_0 = \max(y) - t_0$$

$$\mu_{0,k} = \frac{\sum_{i=1}^{N_{inh}} (y_i - t_0)^2 x_{k,i}}{\sum_{i=1}^{N_{inh}} (y_i - t_0)^2}$$

$$\sigma_{0,k} = \sqrt{\frac{\sum_{i=1}^{N_{inh}} (y_i - t_0)^2 (x_{k,i} - \mu_k)^2}{\sum_{i=1}^{N_{inh}} (y_i - t_0)^2}}$$

$$\sigma_y = \sqrt{\frac{\sum_{i=1}^{N_{inh}} (y_i - \bar{y}_{inh})^2}{N_{inh} - 1}}$$

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Figure 4D

Gaussian Optimization Function

$$f(x) = t + he^{-\sum_{k=1}^{N_x} (x_k - c_k)^2 / 4w_k^2}$$

$$f_o = s_y \left(\frac{\sum_{i=1}^{N_r} u_i (f(x_i) - y_i)^2}{\sigma_y^2 \sum_{i=1}^{N_r} u_i} \right)$$

$$+ s_c \sum_{k=1}^{N_x} \frac{(c_k - c_{0,k})^2}{\sigma_{x_k}^2}$$

$$+ s_w \sum_{k=1}^{N_x} \frac{\sigma_{x_k}}{w_k}$$

$$+ s_t \frac{(t - t_0)^2}{\sigma_y^2}$$

Weighted Mean Squared Error

Center Constraint

Width (Focus) Constraint

Tare Constraint

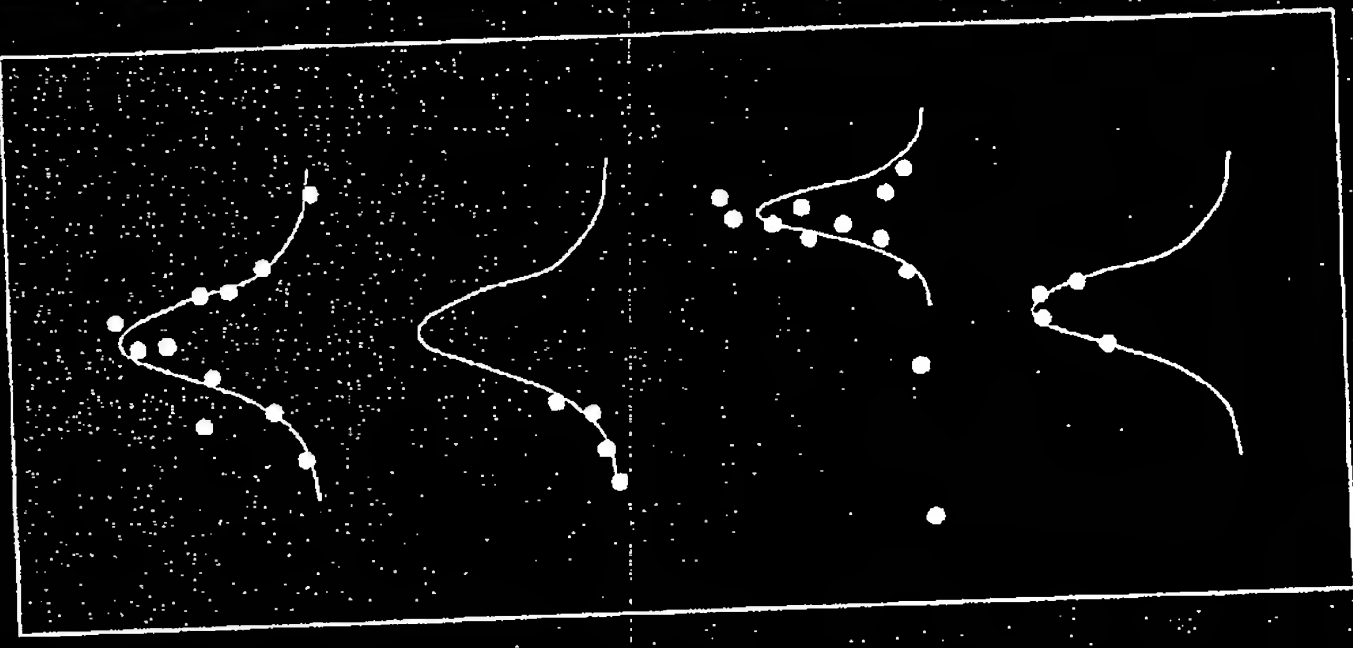


Figure 4E

Gaussian Optimization Starting Values

$$\sigma_y^2 = \frac{\sum_{i=1}^{N_{mh}} u_i (y_i - \bar{y})^2}{\sum_{i=1}^{N_{mh}} u_i}$$

$$t_0 = \min(y)$$

$$h_0 = \max(y) - t_0$$

$$\sigma_{x_k}^2 = \frac{\sum_{i=1}^{N_{mh}} u_i (x_{k,i} - \bar{x}_k)^2}{\sum_{i=1}^{N_{mh}} u_i}$$

$$v_i = \frac{(y_i - t_0)^2}{\sigma_y^2}$$

$$c_{0,k} = \frac{\sum_{i=1}^{N_{mh}} u_i v_i x_{k,i}}{\sum_{i=1}^{N_{mh}} u_i v_i}$$

$$w_{0,k}^2 = \frac{\sum_{i=1}^{N_{mh}} u_i v_i (x_{k,i} - c_{0,k})^2}{\sum_{i=1}^{N_{mh}} u_i v_i}$$

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Figure 4F

Performance Metrics

$$n_k = \frac{\sigma_{y_k}}{w_k}$$

Descriptor Focus

$$S = \sqrt{\frac{\sum_{i=1}^{N_y} u_i (f(x_i) - y_i)^2}{\sum_{i=1}^{N_y} u_i}}$$

Standard Error

$$r^2 = \frac{\left(\sum_{i=1}^{N_y} u_i (f(x_i) - \bar{f}(x)) (y_i - \bar{y}) \right)^2}{\sum_{i=1}^{N_y} u_i (f(x_i) - \bar{f}(x))^2 \sum_{i=1}^{N_y} u_i (y_i - \bar{y})^2}$$

Correlation Coefficient

$$q^2 = 1 - s^2 / \sigma_y^2$$

Residual Error

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Figure 46

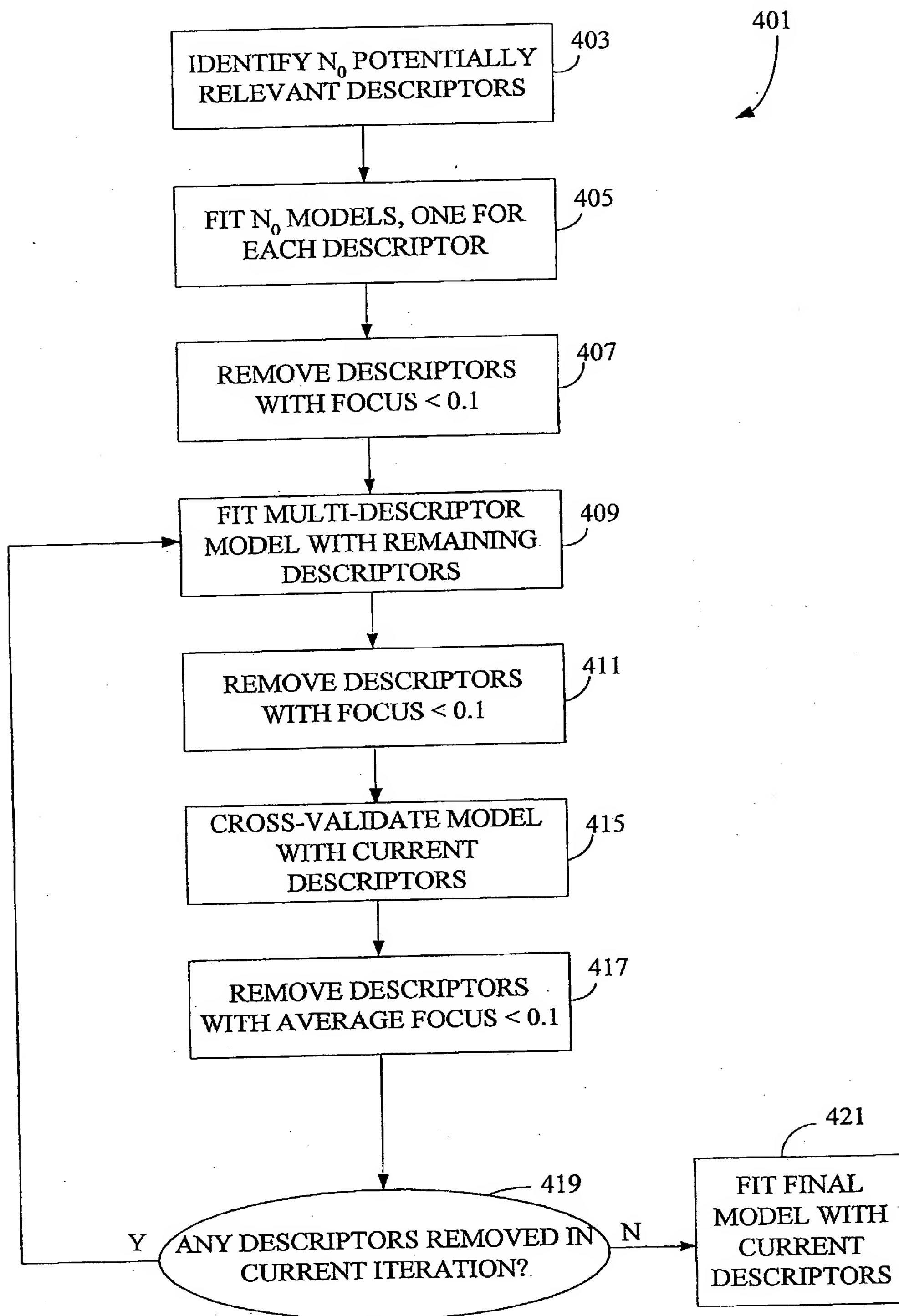


Figure 4H

Sigmoid Optimization Function

$$f(x) = t + \frac{h}{1 + \sum_{k=1}^{N_y} e^{-n_k(x_k - c_k)}}$$

$$f_o = s_y \left[\frac{\sum_{i=1}^{N_y} u_i (f(x_i) - y_i)^2}{\sigma_y^2 \sum_{i=1}^{N_y} u_i} \right]$$

Weighted Mean Squared Error

$$+ s_c \sum_{k=1}^{N_x} \frac{(c_k - c_{0,k})^2}{\sigma_{x_k}^2}$$

Center Constraint

$$+ s_n \sum_{k=1}^{N_x} |n_k| \sigma_{x_k}$$

Focus Constraint

$$+ s_t \frac{(t - t_0)^2}{\sigma_t^2}$$

Tare Constraint

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Figure 4I

Sigmoid Optimization Starting Values

$$t_0 = \min(y)$$

$$h_0 = \max(y) - t_0$$

$$v_i = \frac{(y_i - t_0)^2}{\sigma_y^2}$$

$$v'_i = \frac{(h_0 + t_0 - y_i)^2}{\sigma_y^2}$$

$$c_{h,k} = \frac{\sum_{i=1}^{N_{inh}} u_i v_i x_{k,i}}{\sum_{i=1}^{N_{inh}} u_i v_i}$$

$$c_{l,k} = \frac{\sum_{i=1}^{N_{inh}} u_i v'_i x_{k,i}}{\sum_{i=1}^{N_{inh}} u_i v'_i}$$

$$c_{0,k} = \frac{c_{h,k} + c_{l,k}}{2}$$

$$w_{h,k} = \sqrt{\frac{\sum_{i=1}^{N_{inh}} u_i v_i (x_{k,i} - c_{h,k})^2}{\sum_{i=1}^{N_{inh}} u_i v_i}}$$

$$w_{l,k} = \sqrt{\frac{\sum_{i=1}^{N_{inh}} u_i v'_i (x_{k,i} - c_{l,k})^2}{\sum_{i=1}^{N_{inh}} u_i v'_i}}$$

$$n_{0,k} = \frac{c_{h,k} - c_{l,k}}{w_{h,k} w_{l,k}}$$

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Figure 4J

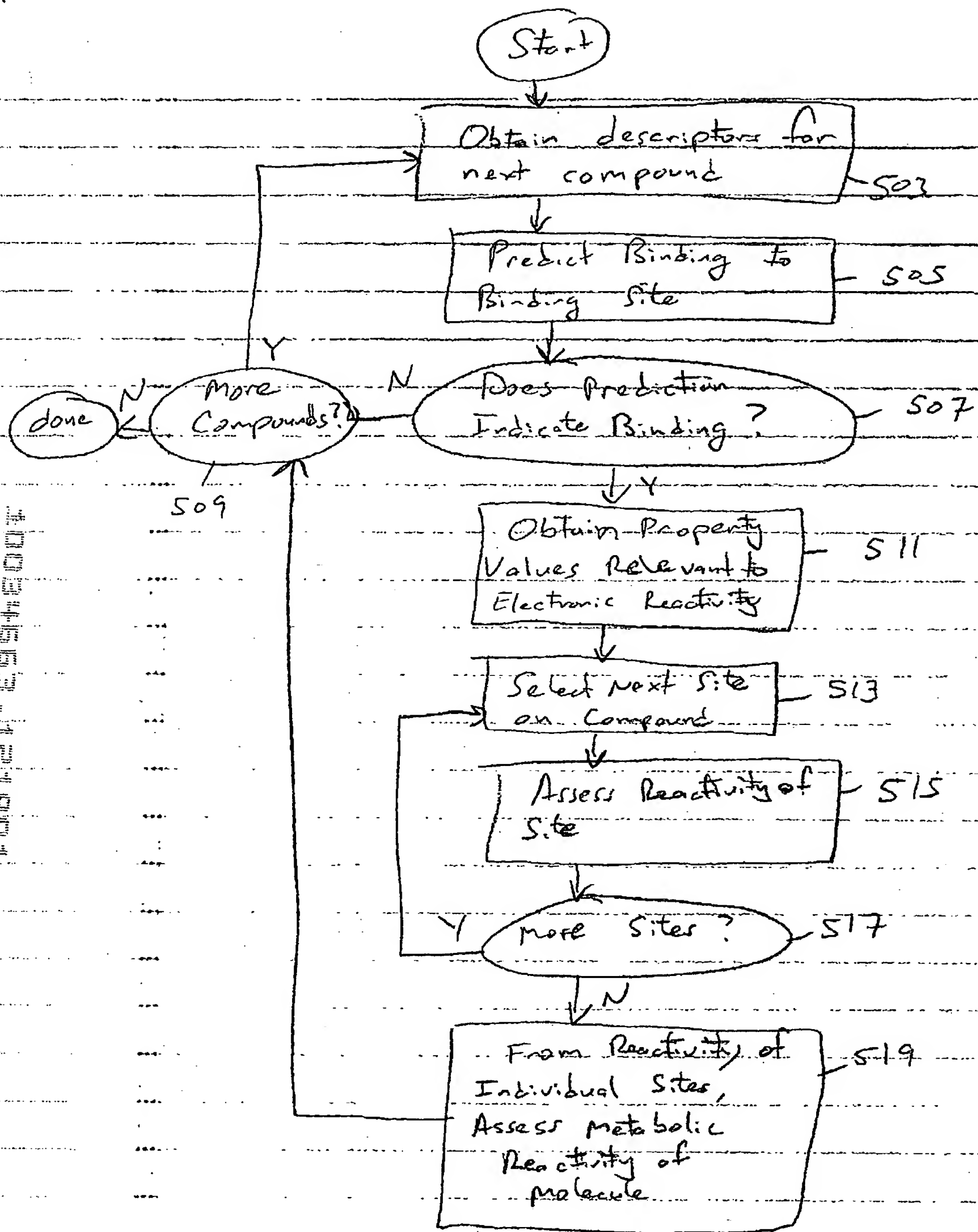


Figure 5.

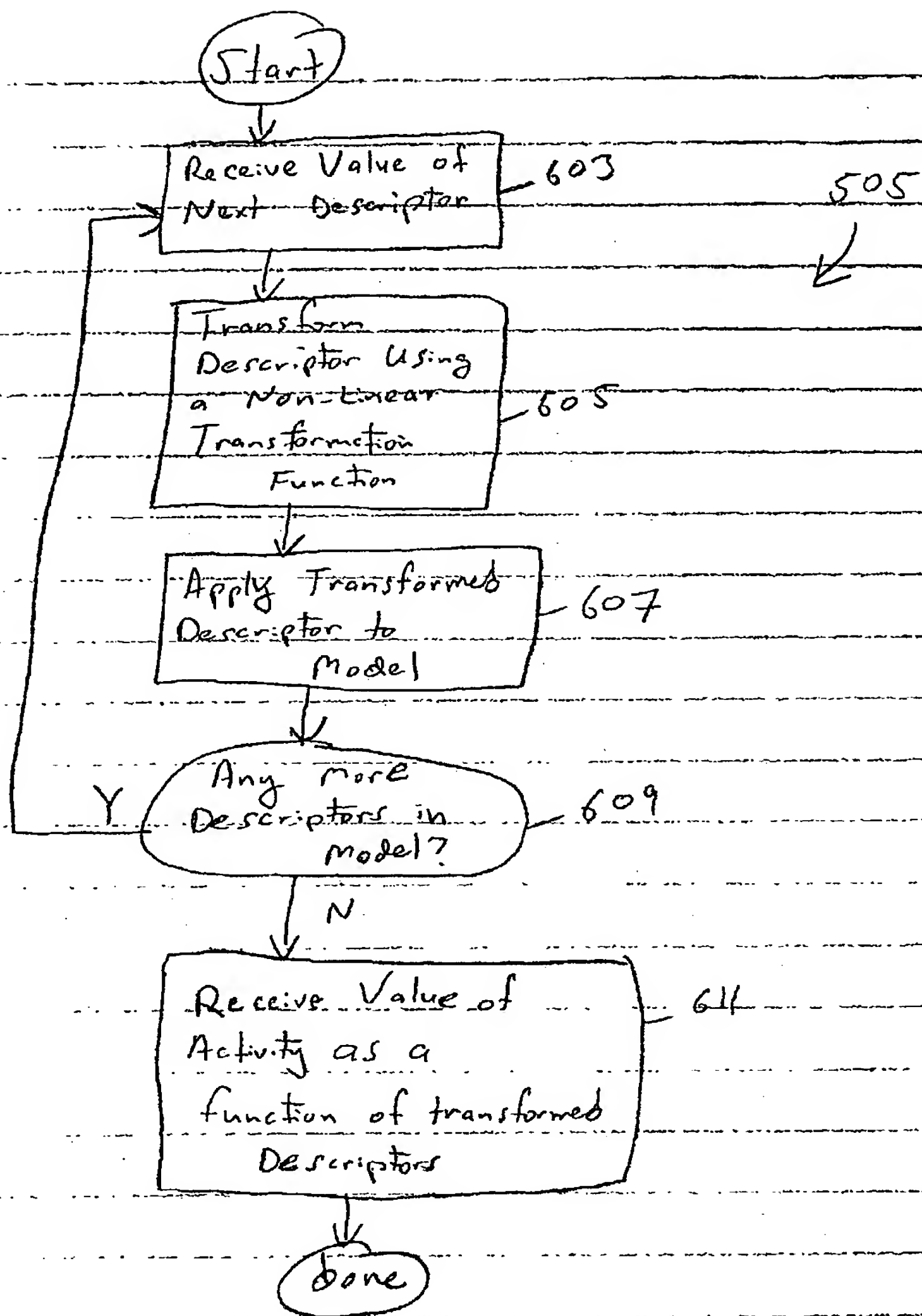


Figure 6

TEST "E94E00"

Optimum logP

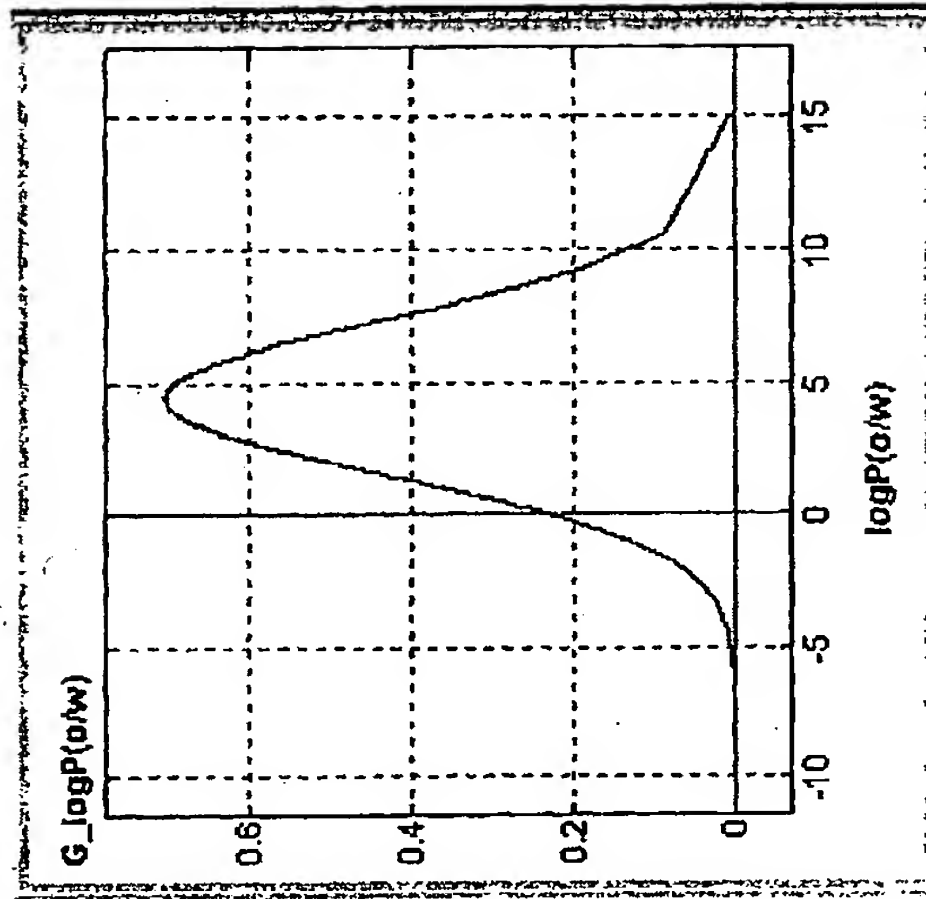
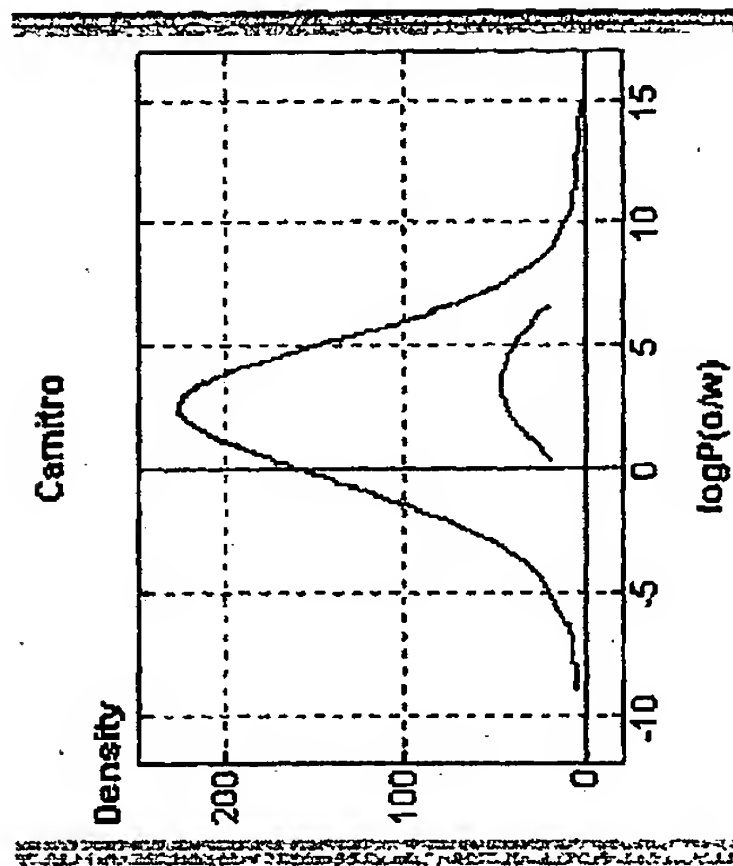


Figure 7A

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FOR "Estate"

Optimum Formal Charge

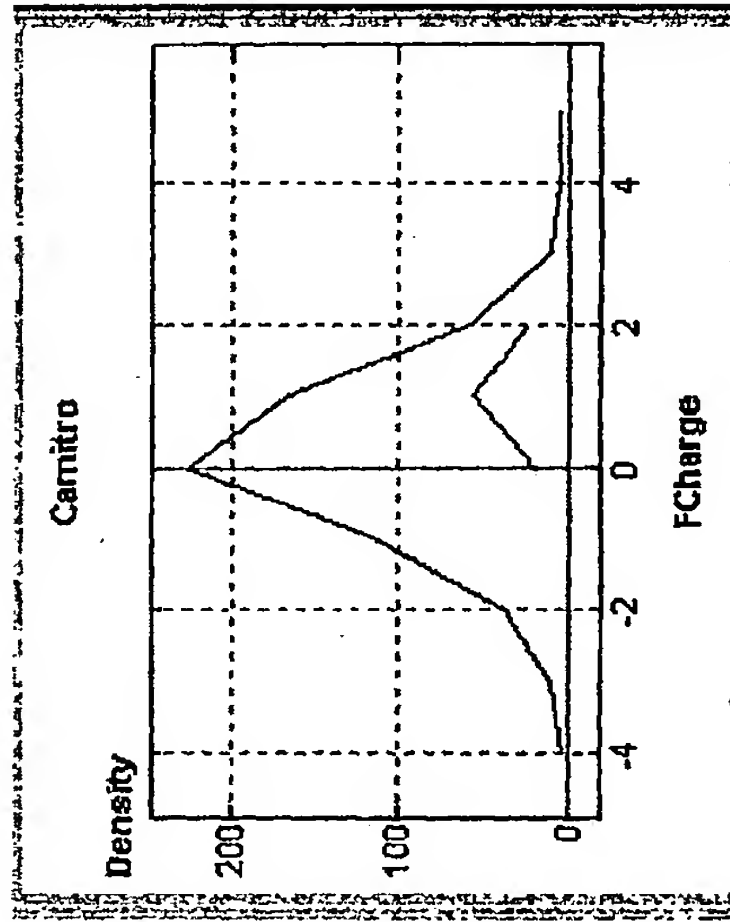
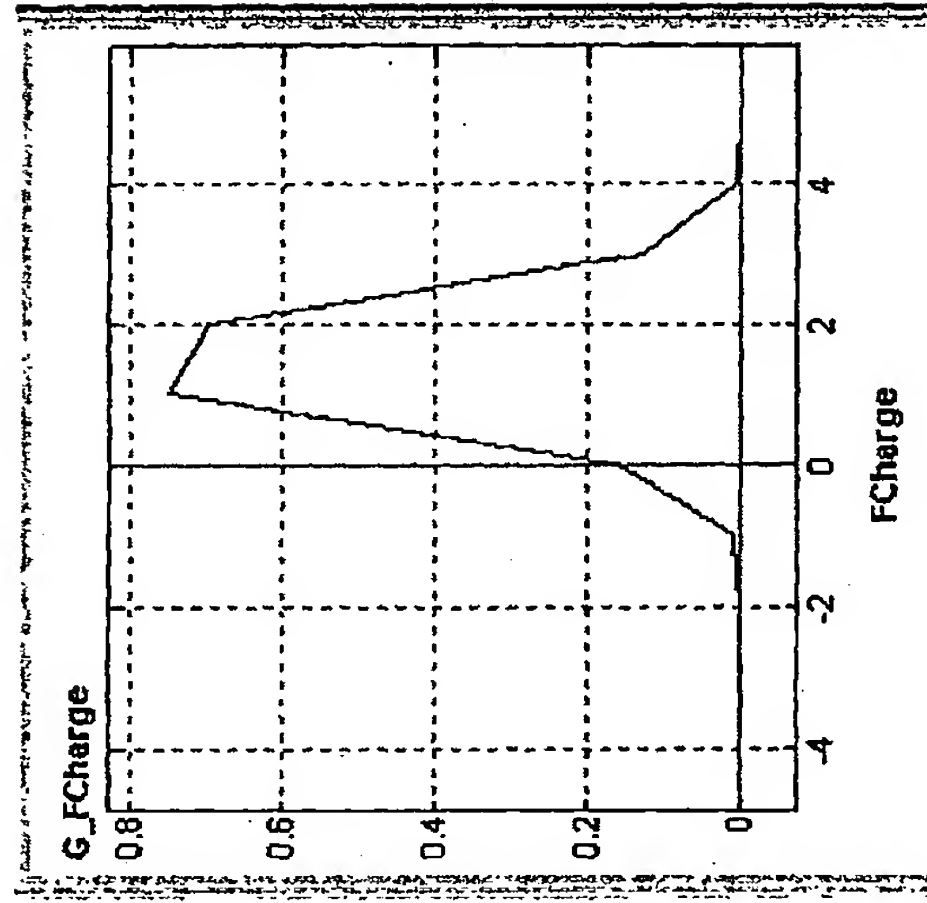


Figure 7B

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FORMAT: E994E007

Automated Gaussian Fit

Database Viewer : f:/2d6/discrim/01/dac-4.mdb

Field Control Display Window: F9

	active	MW	PEOE_VSA_FHYD	PEOE_VSA_FNEG	PEOE_VSA_FPNEG	PEOE_VSA_FPOS	PEOE_VSA_FPPOS
1	0	130.0780	0.5071	0.3361	0.2331	0.6639	0.2598
2	0	136.0430	0.5670	0.7154	0.4330	0.2846	0.0000
3	0	139.1540	0.7499	0.5756	0.1330	0.4244	0.1171
4	0	146.1460	0.5387	0.3008	0.3008	0.6992	0.1605
5	0	148.2740					
6	0	150.2700					
7	0	158.1570					
8	0	160.1800					
9	1	176.2430					
10	0	178.2750					
11	1	179.3320					
12	0	180.1560					
13	0	180.2040					
14	1	180.2710					
15	1	180.2710					
16	0	180.3150					

Database Viewer : f:/2d6/discrim/01/gauss-4.mdb

Field Control Display Window: F9

	Field	Center	Width	Height	rmsc	fress	r2
1	PROB_VSA_FPMRG	0.0311	0.0310	0.8555	0.3764	0.4333	0.5369
2	FCharge	1.4844	0.5524	0.8927	0.3899	0.3918	0.0002
3	PROB_VSA_FHYD	0.9182	0.0741	0.7745	0.4176	0.3025	0.4645
4	PROB_VSA-5	5.1460	5.5009	0.8250	0.4201	0.2941	0.4173
5	PROB_VSA-6	5.7300	9.7930	0.6950	0.4292	0.2630	0.3797
6	a_acc	0.5577	2.1359	0.7321	0.4368	0.2368	0.4760
7	a_base	1.9562	0.8965	0.8122	0.4438	0.2123	0.1308
8	a_acid	0.0000	0.0000	0.5993	0.4476	0.1986	0.2228
9	logP(o/w)	4.4390	2.0997	0.7072	0.4484	0.1956	0.1405

Database Viewer : f:/2d6/discrim/01/dac-4.mdb

Field Control Display Window: F9

	active	MW	PEOE_VSA_FHYD	PEOE_VSA_FNEG	PEOE_VSA_FPNEG	PEOE_VSA_FPOS	PEOE_VSA_FPPOS
1	0	130.0780	0.5071	0.3361	0.2331	0.6639	0.2598
2	0	136.0430	0.5670	0.7154	0.4330	0.2846	0.0000
3	0	139.1540	0.7499	0.5756	0.1330	0.4244	0.1171
4	0	146.1460	0.5387	0.3008	0.3008	0.6992	0.1605
5	0	148.2740					
6	0	150.2700					
7	0	158.1570					
8	0	160.1800					
9	1	176.2430					
10	0	178.2750					
11	1	179.3320					
12	0	180.1560					
13	0	180.2040					
14	1	180.2710					
15	1	180.2710					
16	0	180.3150					

Database Viewer : f:/2d6/discrim/01/gauss-4.mdb

Field Control Display Window: F9

	Field	Center	Width	Height	rmsc	fress	r2
1	PROB_VSA_FPMRG	0.0311	0.0310	0.8555	0.3764	0.4333	0.5369
2	FCharge	1.4844	0.5524	0.8927	0.3899	0.3918	0.0002
3	PROB_VSA_FHYD	0.9182	0.0741	0.7745	0.4176	0.3025	0.4645
4	PROB_VSA-5	5.1460	5.5009	0.8250	0.4201	0.2941	0.4173
5	PROB_VSA-6	5.7300	9.7930	0.6950	0.4292	0.2630	0.3797
6	a_acc	0.5577	2.1359	0.7321	0.4368	0.2368	0.4760
7	a_base	1.9562	0.8965	0.8122	0.4438	0.2123	0.1308
8	a_acid	0.0000	0.0000	0.5993	0.4476	0.1986	0.2228
9	logP(o/w)	4.4390	2.0997	0.7072	0.4484	0.1956	0.1405

Figure 7C

2D6 K_i Model

Non-linear Size Relation

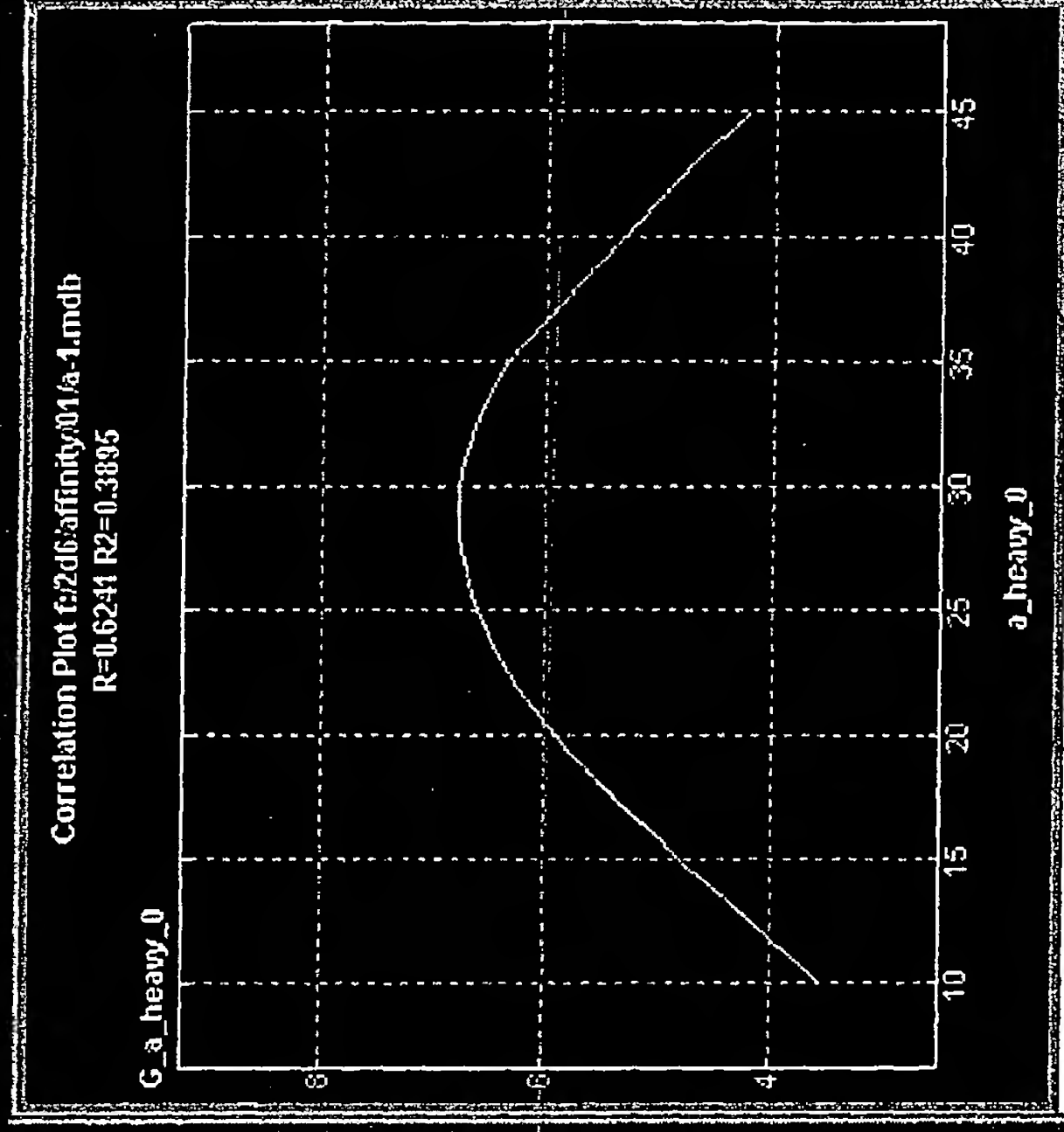
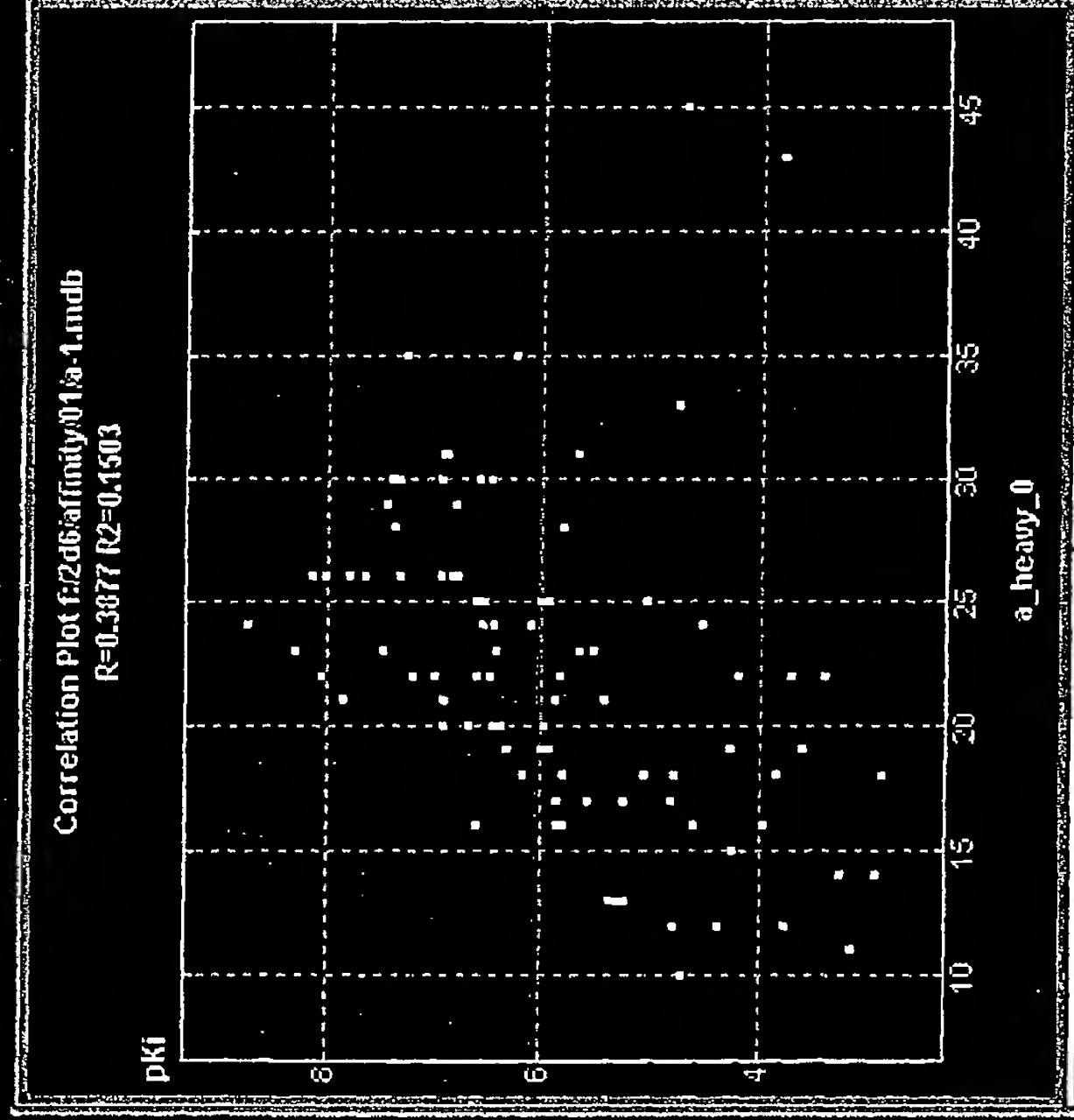


Figure 7D

10/11

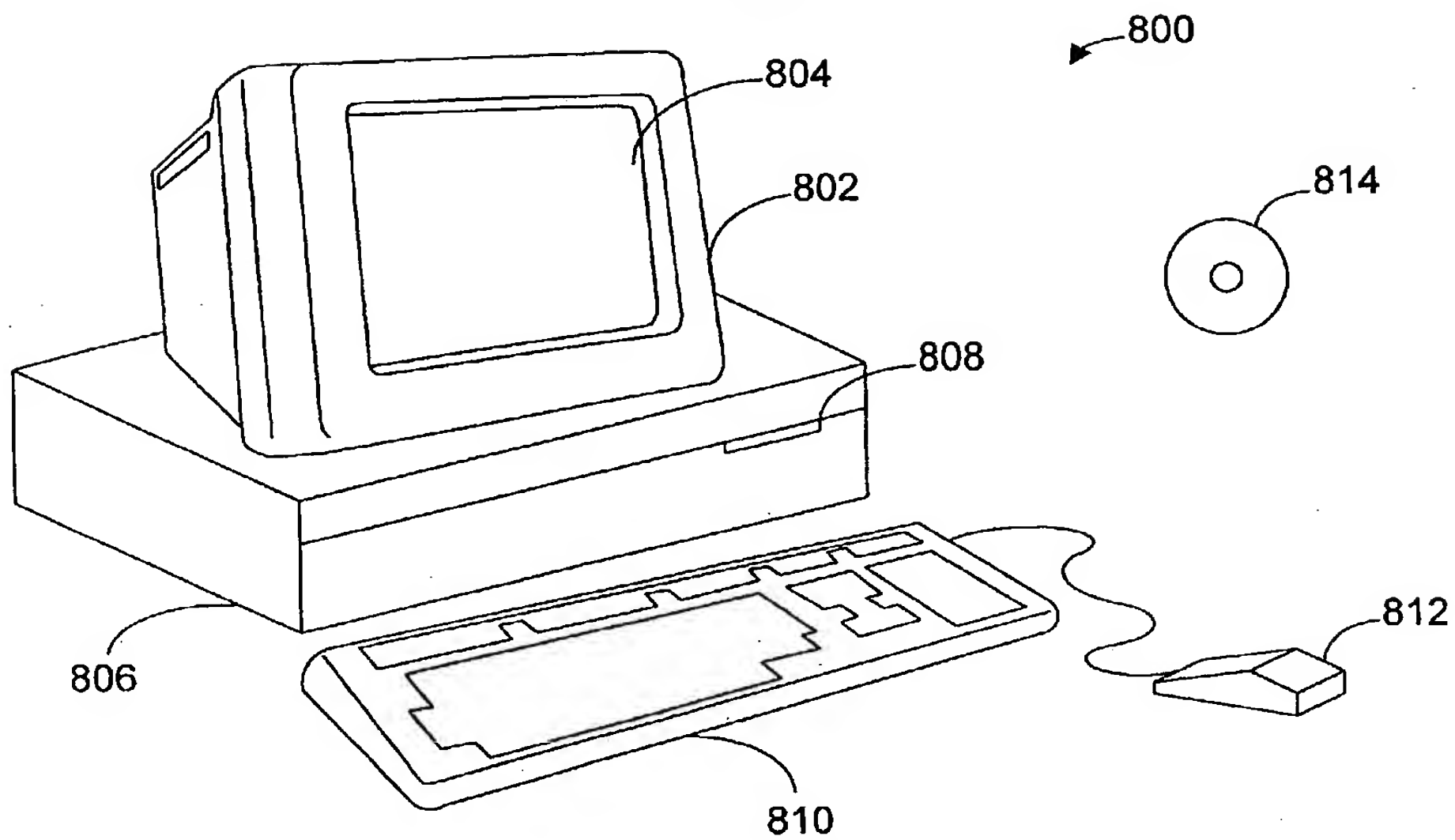


Figure 8A

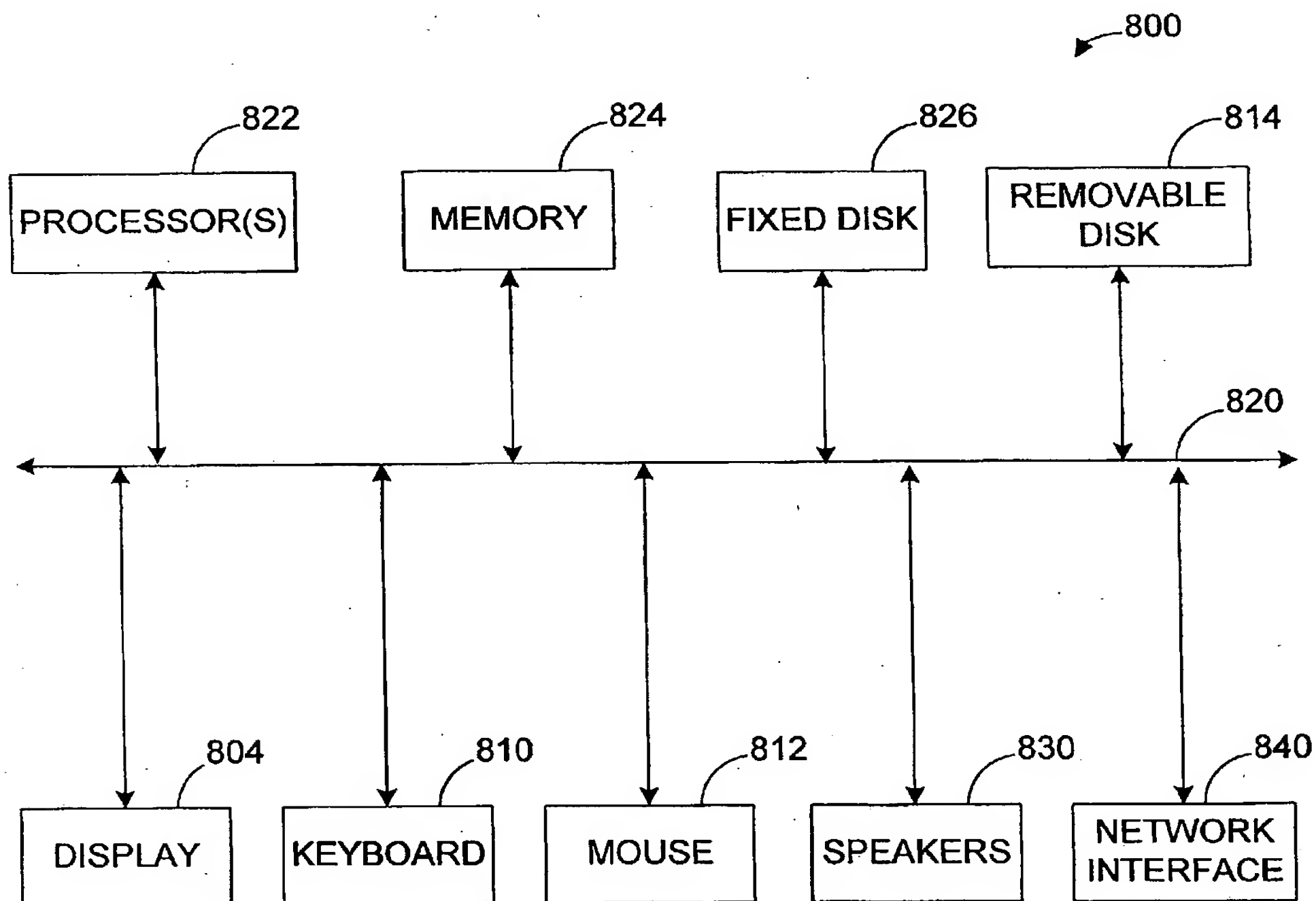


Figure 8B

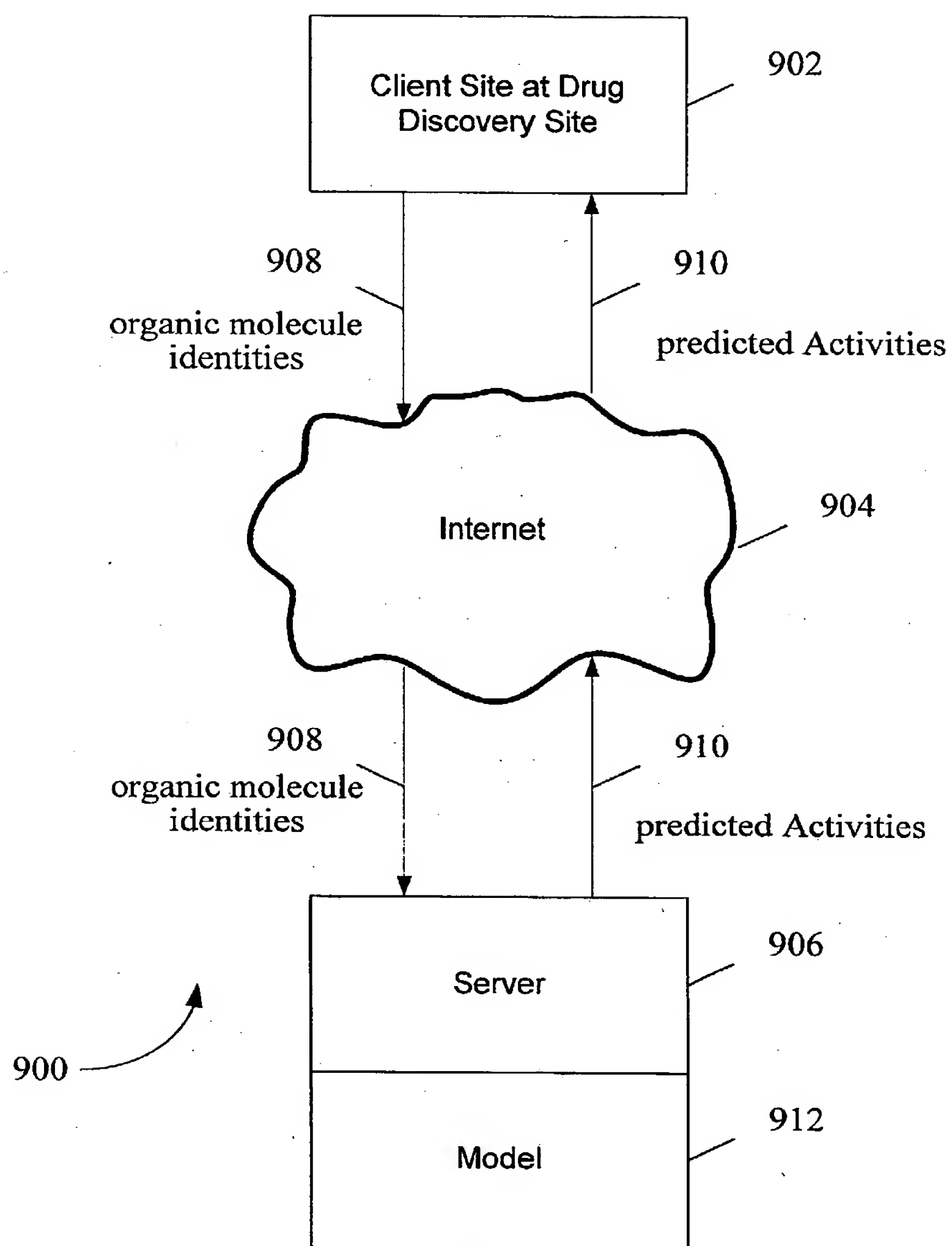


FIGURE 9